PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X16757

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) 12OCT2005
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/000013	10.01.2005	12.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07K16/00, A61K39/395

Applicant
APPLIED MOLECULAR EVOLUTION, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III *Non-establishment of opinion with regard to novelty, inventive step and industrial applicability*
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI *Certain documents cited*
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will *not be so considered*.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Griesinger, I Telephone No. +49 89 2399-7596

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

   see separate sheet

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 17,18

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☒ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☒	has not been furnished
	☐	does not comply with the standard
the computer readable form	☒	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5
	No:	Claims	1,2,6-16,19
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-16,19
Industrial applicability (IA)	Yes:	Claims	1-16,19
	No:	Claims	none

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Introduction

The application relates to antibodies comprising a variant in the Fc region or a portion thereof, wherein at least one of the positions 247, 251, 256, 268, 280, 330, 332, 339, 378, and 440 is modified. The variants were characterized in an antibody-dependent cell-mediated cytotoxicity (ADCC) assay (example 1), for B cell depletion (example 2), for their affinity to Fc-gamma RIIIa (example 3), complement dependent cytotoxicity (CDC, Example 4), binding of the Fc neonatal receptor (FcRn, example 5), and theoretically for their efficiency in the treatment of tumours (example 6). Table 2 shows that each substitution has a different effect, wherein some variants had increased activity and/or affinity and others decreased activity and/or affinity.

The present communication refers to the following documents (D) cited in the international search report. However, the Applicant is warned that the documents cited in the search report and in the present communication are just examples of numerous documents having a similar teaching.

D1: WOLFENSTEIN-TODEL C ET AL: "THE AMINO-ACID SEQUENCE OF HEAVY CHAIN DISEASE PROTEIN ZUC STRUCTURE OF THE FC FRAGMENT OF IMMUNO GLOBULIN G-3" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 71, no. 4, 1976, pages 907-914, XP009046941 ISSN: 0006-291X

D2: US 2004/002587 A1 (WATKINS JEFFRY D ET AL) 1 January 2004 (2004-01-01)

D3: US-B1-6 277 375 (WARD ELIZABETH SALLY) 21 August 2001 (2001-08-21)

D4: (PX document): WO 2004/063351 A (MACROGENICS, INC; STAVENHAGEN, JEFFREY; VIJH, SUJATA) 29 July 2004 (2004-07-29)

D1 discloses the amino acid sequence of the Fc domain of human IG3. The sequence according to Fig. 2a seems to be 100% identical to the sequence according to Seq. ID No. 29 (variant A339T) of the present application.

D2-D4 disclose variants of the Fc domain of antibodies and their effect on the immune reaction, such as ADCC assays. D2 discloses variants at position 280, D3 at position 256,

D4 (PX document) at positions 256, 330, 332, and 339.

Re Item III

Non establishment of opinion with regard to novelty, inventive step and industrial applicability

For the reasons indicated in the international search report, the subject-matter of claims 17 and 18 can not be searched and examined. The same applies for claim 19 as far as said claim refers to the subject-matter of claims 17 and 18.

Re Item IV

Lack of unity of invention

The application as filed is considered to lack unity of invention since its subject-matter relates not to one but rather to ten separate inventions not linked together by a common underlying inventive concept as required by Rule 13.1 PCT.

The claims and the inventions to which the ten separate inventions relate may be grouped as indicated in the international search report.

According to Rule 13.2 PCT, an international patent application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Unity of invention is fulfilled only when there is a technical relationship among the inventions involving one or more of the same or corresponding special technical features. Special technical features are such features that define the contribution of the claimed invention over the prior art.

The identified ten inventions involve the technical feature of "antibodies comprising a variant of the Fc region or a portion thereof". However, this feature cannot be accepted to constitute a special technical feature because it does not define a contribution over the prior art. D1 already discloses a sequence which is 100% identical to the sequence according to Seq. ID No. 29, which corresponds to the variant "A339T" (see Table 2 of the description). Hence, said feature is not novel in view of D1. Furthermore, said technical feature is also not novel in view of numerous other documents such as e.g. D2 and D3,

which also disclose variants of the Fc domain of antibodies. Consequently, the feature of "antibodies comprising a variant of the Fc region or a portion thereof" can not be accepted as the common inventive concept.

The contributions claimed in the present application which are allegedly made over the prior art are:

a) for the first group the substitution of the amino acid 247 of the Fc region;

b)-j) for the second to tenth group respectively the substitution of the amino acid 251, 256, 268, 280, 330, 332, 339, 378, and 440 of the Fc region;

These contributions are not so linked as to form one single inventive concept (Rule 13.1 PCT).

In summary, the ten inventions correspond to the ten variable positions claimed in claim 1. Variants having more than one amino acid substitution such as e.g. a substitution at position 247 and 251, belong to both groups, i.e. in this case to groups 1 and 2.

Since the additional effort searching all inventions did not justify a further search fee, the search report was drawn up for all ten inventions. However, during examination procedure, a lack of unity objection has to be expected.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Novelty

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 2, 6-16, and 19 is not new in the sense of Article 33(2) PCT.

D1 discloses antibodies comprising the variant A339T, D2 variants at position 280 and D3

at position 256. Consequently, the subject-matter of claim 1 is not novel in view of either D1 or D2 or D3 and the subject-matter of claim 2 is not novel in view of D1.

Claims 6-11 refer to the characteristics of the antibodies comprising said variants, namely the ADCC specific activity and mediation of CDC. However, said characteristics seem to be inherent to the antibodies due to the amino acid substitutions. Since the discovery of a property of a product can not make the product novel, the additional features of claims 6-11 can not make the subject-matter of the claims novel. Furthermore, it seems that the properties of said variants were also known (see e.g. example 4 of D4) so that a method claim also does not seem to be allowable.

Claims 12-16 are not novel, since the claimed types of antibodies are already disclosed in the prior art (see e.g. paragraphs 3-10 of D2).

The scope of a claim directed to a pharmaceutical composition comprising the antibodies according to the present application, comprises antibody solutions in water or buffer. Hence, the subject-matter of claim 19 is not novel in view of any of the documents D1-D3.

2. Inventive step

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of all claims does not involve an inventive step in the sense of Article 33(3) PCT.

Even if the novelty objections of the previous paragraphs were overcome by limiting the claims to variants, which are not specifically disclosed in the prior art, said variants would not be considered to be inventive. In view of the numerous variants already known from prior art documents (such prior art documents are so frequent, that only a selection of documents could be cited in the present international search report and in the communication), the provision of further variants can not be considered to be inventive. It seems that the specific variants characterized by a Seq. ID Nos. have no technical feature and/or property clearly distinguishing them from the variants known from the prior art. Therefore, the variants seem to be an arbitrary selection from all possible variants of the Fc region of an antibody (see also objections under Articles 5 and 6 PCT).

Re Item VI

Certain documents cited

The document D4 has not been considered in the present communication, since it was published after the priority date of the present patent application and regulations concerning such "PX" documents differ between the PCT member states. However, the document may be relevant for accessing novelty and inventive step of the present application.

Re Item VII

Certain defects in the international application

1. In the description of the present application, reference is made to figures (see e.g. page 120, line 1 to page 121, line 25). However, no figures have been received when the application was filed. Furthermore, in the PCT request the number of drawings is indicated as "0". Consequently, it seems to be necessary to delete all references to the figures in the description.

2. Claims 17 and 18 refer to a sequence according to Seq. ID No. 57 and 58. However, neither the electronic nor the paper version of the sequence listing comprise said sequences. The last Seq. ID No. in the sequence listing is 56. Hence, claims 17 and 18 do not comply with the requirements of Rule 13ter PCT. Furthermore, neither from the claims nor from the description the subject-matter of said claims can be deduced. Therefore, the subject-matter of the claims is not sufficiently disclosed and so unclear, that no search and examination can be performed (Articles 5 and 6 PCT). Therefore, all references in the claims and in the description to said sequences should be deleted.

Re Item VIII

Certain observations on the international application

1. The subject-matter of claims 1-16 and 19 is unclear, since the antibody is only defined by reference to "human Fc region" and an amino acid position. Although the human Fc region is well known in the art (see e.g. D1), the numbering of the amino acids is not always identical in the prior art documents. Hence, the definition of the antibody or

the portion thereof does not seem to be clear (Article 6 PCT). Furthermore, it seems that the indication of the position of a substituted amino acid is not sufficient, but the exact substitution is needed. Therefore, the subject-matter of claim 1 is also not considered to fulfill the requirements of Article 5 PCT. The objections could be overcome by indicating the Seq. ID No. in addition to the exact amino acid substitution.

2. Claims 6-11 not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result (see also novelty objection).